Title: A systematic review and meta-analysis of the use of renin-angiotensin system drugs and COVID-19 clinical outcomes: What is the evidence so far?

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Running title: Renin-angiotensin system drugs and COVID-19

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Abbreviations and Acronyms

ACEIs: Angiotensin-Converting Enzyme Inhibitors; ACE2: Angiotensin-Converting Enzyme 2; ARBs: Angiotensin Receptor Blockers; AT_1R: Angiotensin Receptor 1; CVD: Cardiovascular Disease

Abstract

Conflicting evidence exist about the effects of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin-receptor blockers (ARBs) on COVID-19 clinical outcomes. We aimed to provide a comprehensive/updated evaluation of the effect of ACEIs/ARBs on COVID-19 related-clinical outcomes, including exploration of inter-class differences between ACEIs and ARBs, using a systematic review/meta-analysis approach conducted in Medline (OVID), Embase, Scopus, Cochrane library and medRxiv from inception to 22nd May 2020. English studies that evaluated the effect of ACEIs/ARBs among patients with COVID-19 were included. Studies' quality was appraised using the Newcastle-Ottawa Scale. Data were analysed using the random-effects modelling stratified by exposure (ACEIs/ARBs, ACEIs, and ARBs). Heterogenicity was assessed using I^2 statistic. Several sub-group analyses were conducted to explore the impact of potential confounders. Overall, 27 studies were eligible. The pooled analyses showed non-significant associations between ACEIs/ARBs and death (OR:0.97, 95%CI:0.75,1.27), ICU admission (OR:1.09;95%CI:0.65,1.81), death/ICU admission (OR:0.67; 95%CI:0.52,0.86), risk of COVID-19 infection (OR:1.01; 95%CI:0.93,1.10), severe infection (OR:0.78; 95%CI:0.53,1.15) and hospitalisation (OR:1.15; 95%CI:0.81,1.65). However, the sub-group analyses indicated significant association between ACEIs/ARBs and hospitalisation among USA studies (OR:1.59; 95%CI:1.03,2.44), peer-reviewed (OR:1.93, 95%CI:1.38,2.71), good quality and studies which reported adjusted measure of effect (OR:1.30, 95%CI:1.10,1.50). Significant differences were found between ACEIs and ARBs with the latter being significantly associated with lower risk of acquiring COVID-19 infection (OR:0.24; 95%CI: 0.17,0.34). In conclusion, high-quality evidence exist for the effect of ACEIs/ARBs on some COVID-19 clinical outcomes. For the first time, we provided evidence, albeit of low quality, on inter-class differences between ACEIs and ARBs for some of the reported clinical outcome.

Keywords

Angiotensin-converting enzyme inhibitors; Angiotensin-receptor blockers; COVID-19 infection; Coronavirus; Severe acute respiratory syndrome coronavirus 2

Introduction

Soon after the report of first clusters of COVID-19 cases in China in December 2019, concerns were raised among clinicians and investigators that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) might increase susceptibility to COVID-19 infection and the likelihood of severe and fatal COVID-19 illness [1]. These concerns are based on the concept that angiotensin-converting enzyme 2 (ACE2), an enzyme potentially up-regulated by ACEIs/ARBs use, is the viral entry receptor that COVID-19 uses to enter lung cell [2], coupled with the observation of high prevalence of hypertension and other cardiovascular comorbidities among COVID-19 patients who have poor outcomes [3] . Consequently, it was speculated that due to considerable prescribing of ACEIs/ARBs to treat cardiovascular diseases (CVD), this would adversely affect outcomes from COVID-19 [4] with underlying cardiac and kidney diseases already associated with poorer outcomes [3,5,6]. Consequently, care to avoid treatments that well add to this.

Unsurprisingly, discussions regarding the potential impact of ACEIs/ ARBs has resulted in anxiety, which might cause patients and clinicians to discontinue or stop these medications [7] . This should be avoided as there will be harm from the indiscriminate withdrawal of ACEIs/ARBs [8]. This concern is complicated by uncertainty surrounding the up-regulation of ACE2 by ACEIs/ARBs [9]. Furthermore, the paradoxical protective role of ACEIs/ARBs in COVID-19 patients is also being proposed [10]. Due to these controversial findings, and despite consistent and reassuring recommendations for the continued use of ACEIs/ARBs in COVID-19 patients issued by International Societies [11], these concerns remain. We wish to address this as we have already seen the impact that inappropriate endorsement of treatments can have on morbidity and mortality. Early endorsement of hydroxychloroquine resulted in drug shortages for other indications, price hikes, increased adverse drug reactions and deaths from suicides [12,13]. However, subsequent studies failed to show clinical benefit resulting in the World Health Organisation (WHO) and the National Institute of Health (NIH) in the USA stopping the hydroxychloroquine arm in their studies [14-16]. A similar situation has been seen with lopinavir/ritonavir[15]. Consequently it is imperative that any considerations regarding management are evidenced based.

We are aware that several observational studies have been conducted to address these concerns. However, these studies have reported conflicting findings which is a concern given the controversies with hydroxychloroquine and lopinavir/ritonavir. For instance, some studies [17-22] have reported a lower risk of severe COVID-19 outcomes with ACEIs/ARBs whilst another study [23] found a higher risk. Similarly, ACEIs/ARBs have been associated with lower mortality rates in some studies [17,20,24-27] whilst others [23,28] reported higher mortality rates. We are also aware that two recently published systematic reviews [29,30] containing 16 studies reported no evidence of any association between ACEIs/ARBs and mortality, severe COVID-19 outcomes, or acquiring COVID-19 infection; however, these studies only analysed a limited range of outcomes, and did not report the effects of ACEIs and ARBs individually. The authors also

did not undertake any sub-group analysis to explore the effect of potential confounders such as study's quality and there are concerns that the findings may now be out-dated. Furthermore, one of these studies [30] only used narrative synthesis of the data. Consequently, we sought to undertake an updated and comprehensive evaluation of effect of ACEIs/ARBs use on all reported COVID-19 related outcomes, including exploration of any class differences, through a systematic review of the literature coupled with a meta-analysis.

Methods

Data Source and Searches

This systematic review and meta-analysis was conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist [32]. A protocol was drafted and shared with authors but not registered in any database as we did not want the submission of our findings be delayed until the study protocol was registered as we wanted to provide the clinical community with a timely publication of the available evidence whether published in peer-reviewed journals or awaiting publication surrounding the impact of ACEIs/ARBs use on COVID-19 outcomes. The literature search was conducted in Embase, Medline (OVID), Scopus, Cochrane library and medRxiv, from inception to 22nd May 2020, using key terms related to ACEIs/ARBs and COVID-19 concepts. A detailed electronic search strategy used in the database searches is attached [Supplementary file 1]. We also manually searched the reference list of eligible articles to identify any further relevant articles.

Study Selection

Eligibility criteria included original research studies, published in English, with COVID-19 patients (target population) that reported the effects of ACEIs/ARBs (intervention), in comparison with non ACEIs/ARBs use (comparison), on COVID-19 related outcomes. No restrictions were placed on the reported outcomes or study types. All records identified from the search strategy were exported from the databases and imported into Covidence® [31] whereby duplicate records were removed. Two reviewers (NA and LA) independently undertook titles and abstract screening for relevance, followed by selecting records for full-text screening and data extraction. At each stage, discrepancies were resolved through discussion until consensus was achieved. A third author (AK) verified the eligibility of the included studies.

Data Extraction and Quality Assessment

Data from the eligible studies were subsequently extracted by two authors (NA, AK) into a spreadsheet including information on the study characterises (study design, setting, sample size, population, exposure-ACEIs/ARBs, ACEIs, or ARBs) and outcome measures including death, intensive care unit (ICU) admission, risk of COVID-19 infection, severe COVID-19 infection, severe pneumonia, hospitalisation, hospital discharge, use of ventilators, duration of hospital stay, septic shock, acute kidney injury, cardiac injury, and hospital readmission. Since the need for using ventilators typically necessitates ICU admission,

we combined studies that reported ICU admission and ventilator use as a further composite outcome measure. Two authors (NA and LA) independently conducted the assessment of risk of bias using the Newcastle-Ottawa Scale (NOS) for nonrandomised studies which consists of three domains (selection of participants and control (if applicable), comparability and exposure or outcome) [32], whereby studies were classified into good quality (3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain), fair quality (2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain) and poor quality (0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain) [33]; any disagreement between the two reviewers (NA and LA) was resolved by involving a third researcher (AK) for discussion until a consensus was reached .Furthermore, interrater reliability measures such as kappa statistic and percentage agreement were also calculated. Some of the co-authors have used this approach before [34].

Data Synthesis and Analysis

For each study outcome that was reported by more than one study, the results from individual studies were combined statistically using the random-effects meta-analysis model, stratified by the level of exposure (ACEIs/ARBs, ACEIs, ARBs); whereas for outcomes which were reported by only one study, narrative synthesis was used. For studies which did not report the summary statistics and measure of effects, we firstly used the reported primary statistics (number of patients with/without the outcomes in both exposed/unexposed group) to calculate the corresponding measure of effects (Odds ratios- OR) and their 95% confidence interval (95%CI) [35], and subsequently used these measure of effects in the random-effects meta-analysis; random-effects model was used as it is considered the most appropriate model by most researchers since it allows the results to be generalisable to other populations as well as addresses the likely heterogeneity between the included studies [36]. Several sub-group analyses were also undertaken to explore the effect of potential confounders on the robustness and sensitivity of combined pooled estimates and included sub-group analyses based on whether the reported measure of effects was crude or adjusted, the study was peer-reviewed or not, the study's methodological quality as per the risk of bias assessment was performed as well as the continent where the study was conducted. Meta-analyses pooled estimated were presented as odds ratios and 95%CI and graphically as forest plots. Heterogeneity between the studies was evaluated using I^2 statistic [37], indicating whether variability is more likely due to study heterogeneity or chance. Negative I^2 values were set to zero, hence I^2 values ranged between 0%-100% with 0% indicating lack of heterogeneity, whereas 25%, 50%, and 75% indicating low, moderate and high heterogeneity, respectively [37]. Publication bias was assessed using funnel plots and Egger's asymmetry test [38] for those outcomes where >10 studies were included in the analysis as recommended by Cochrane guidelines [39]. Data were analysed using STATA 12.

Role of the Funding Source

None

Results

Study characteristics

The literature search identified 452 articles. However, only 27 studies were eligible for inclusion (Figure **1**). A total of 72,372 patients were included in these 27 studies of which 10,197 (14.1%) patients were on ACEIs or ARBs. The average age of the population in these studies was 61±9.6 years and men represented 52.24% of them (Table 1). Twenty-one studies (77.8%) focused on comparing COVID-19 related outcomes between ACEI/ARB users vs. non-users among patients with COVID-19 while the remaining six studies (22.2%) focused on comparing outcomes between ACEIs/ARBs users in patients with and without COVID-19 infection (Table 1). ACEIs/ARBs in the included studies were indicated for a wide range of chronic conditions such as hypertension, coronary artery diseases, heart failure, diabetes or chronic kidney disease.

In terms of outcomes, nine studies (33.3%) reported three to five COVID-19 related outcomes [20,23,25,26,40-44], while another nine studies (33.3%) reported only two outcomes [17,19,22,24,27,45-48] with another one-third reported only one outcome [19,22,29,46-51]. Overall, the 27 studies reported data on 15 unique outcomes including death in 12 studies [18,21,28,49-54], ICU admission in seven studies [23,25,40-44], death/ICU admission as a composite outcome in four studies [21,40,45,54], risk of acquiring COVID-19 infection in nine studies [22,25,26,42-44,48,49,53], risk of severe COVID-19 infection in seven studies [17-19,22,24,48,50], risk of severe pneumonia in two studies [26,51], risk of hospitalisation in eight studies [26,42-47,52], hospital discharge in three studies [23,26,27], use of ventilator in four studies [19,23,41,44], duration of hospital stay in two studies [25,26], and each of acute respiratory distress syndrome (ARDS), septic shock, cardiac shock, acute kidney injury [20], and hospital readmission [23] in one study, respectively. In terms of the exposure, the effects of ACEIs and ARBs were assessed as one class (ACEIs/ARBs) in 17 studies (63%) [17,20,22-28,40,43,44,47,50,51,53,54], as separate classes in five studies (18.5%) 52, 74, 78, 80, 84), and both as one and separate classes in another five studies [18,19,41,45,49].

The majority of the 27 eligible studies were conducted in Asia (44.4%, n=12 with 10 studies from China, one from each of in Korea and Israel), followed by nine studies (33.3%) from Europe (four in Italy, three in the United Kingdom and one from each of France and Belgium) and the remaining six (22.3%) from the USA. Furthermore, the reported measure of effects were crude/un-adjusted measures in the majority of the studies (77.8%, n=21) [18,19,21-28,40-46,48,53,54]; with most of them (59.3%, n=16) being non-peer reviewed articles published as preprints on medRivix [24,26,27,40-43,45-48,50-54], and only four rated as a good quality studies based on the Newcastle-Ottawa Quality Assessment risk of bias [21,40,47,48] (Table 2). Results from the interrater reliability measures indicated a substantial agreement between the two

independent reviewers (NA and LA) in assessing the risk of bias (kappa statistic=0.79; percentage of agreement=89% (24/27)).

Study outcomes

Death and ICU admission

Among pertinent studies, there was insignificant association between mortality and ACEIs/ARBs (OR: 0.97; 95%CI: 0.75 1.27), ACEIs (OR:1.05; 95%CI: 0.75, 1.46), or ARBs (OR:1.18, 95%CI: 0.98, 1.42) (Figure 2; Table 3), regardless of the studies' country, quality, peer-review status or crude/adjusted measure of effect (Supplementary file 2; Table 4). Similarly, there was an insignificant association between ICU admission and ACEIs/ARBs (OR: 1.09; 95%: 0.65, 1.81) and ACEIs (OR:0.95; 95%CI: 0.65, 1.38) but significantly higher odds of ICU admission with ARBs (OR:1.49, 95%CI: 1.13, 1.97) (Figure 3; Table 3). However, sub-group analyses indicated different results. A significantly lower ICU admission rate was associated with ACEIs/ARBs among European studies (OR:0.49; 95%CI: 0.25, 0.97), and good quality studies (OR:0.36; 95%CI: 0.22, 0.59), in contrast to significantly higher ICU admission rate among USA studies (OR:1.59; 95%CI: 1.28, 1.98), peer-reviewed studies (OR:1.56; 95%CI: 1.23, 1.97), and poor quality studies (OR:1.44; 95%CI: 1.13, 1.84) (Supplementary file 3; Table 4). Meta-analysis of the three studies that reported death and ICU admission as a composite endpoint indicated significantly lower odds of death/ICU admission with ACEIs/ARBs use (OR:0.67; 95%CI: 0.52, 0.86) but insignificant lower association with ACEIs (OR:0.89; 95%CI: 0.69, 1.14) or ARBs (OR: 0.83; 95%CI: 0.65, 1.06), regardless of any sub-group analysis for ACEIs and ARBs (Figure 4; Table 3). The sub-group analyses for ACEIs/ARBs, however, showed a significantly lower association of death/ICU admission with ACEIs/ARBs only among European studies (OR: 0.68; 95%CI: 0.52, 0.89), good quality studies (OR:0.63; 95%CI: 0.47, 0.84), and studies which reported adjusted measure of effect (OR:0.63; 95%CI: 0.47, 0.84) (Supplementary file 4; Table 4).

Risk of acquiring COVID-19 infection, severe COVID-19 infection and severe pneumonia

The overall pooled analysis of nine studies indicated insignificant association between the risk of acquiring COVID-19 infection and the use of ACEIs/ARBs (OR: 1.01; 95%CI: 0.93, 1.10), ACEIs (OR: 1.13; 95%CI: 0.9, 1.42), or ARBs (OR: 0.56; 95%CI: 0.11, 2.89) (Figure 5; Table 3). The sub-group analyses results were consistent with overall analyses results for ACEIs/ARBs and ACEIs (Supplementary file 5A; Supplementary file 5B; Table 4) but there were inconsistent for ARBs with a significantly lower risk of acquiring COVID-19 with ARBs among non-peer-reviewed studies, good quality studies and studies which reported crude measure of effects (OR: 0.24; 95%CI: 0.17, 0.34) (Supplementary file 5C; Table 4). Similarly, in a pooled analysis of seven and two studies, insignificant association was observed between the risk of developing severe COVID-19 infection, severe pneumonia, respectively, and ACEIs/ARBs (OR:0.78; 95%CI: 0.53, 1.15; OR:1.29; 95%CI: 0.24, 6.96), ACEIs (OR: 0.72; 95%CI: 0.26, 1.95) or ARBs (OR: 0.51; 95%CI: 0.25, 1.04) (Figure 6; Table 3), regardless of any sub-group analysis (Supplementary file 6; Table 4).

Hospitalisation, hospital discharge and duration of hospital stay

In a pooled analysis of eight and three studies, there was no signification association between hospitalisation, hospital discharge rate and ACEIs/ARBs (OR: 1.15; 95%CI: 0.81, 1.65; OR: 1.21; 95%CI: 0.74, 1.99), ACEIs (OR: 1.08; 95%CI: 0.79, 1.46) or ARBs (OR: 0.91; 95%CI: 0.74, 1.11) (Figure 7; Figure 8Table 3). However, sub-group analyses demonstrated a significantly higher risk of hospitalisation with ACEIs/ARBs among studies conducted in the USA (OR:1.59; 95%CI: 1.03, 2.44), peer-reviewed studies (OR:1.93, 95%CI: 1.38, 2.71), good quality studies and studies which reported adjusted measure of effect (OR:1.30, 95%CI: 1.10, 1.50) (Supplementary file 7; Table 4). Contrastingly, a significantly higher rate of hospital discharge was observed with ACEIs/ARBs but only among non-peer reviewed articles (OR:1.51; 95%CI: 1.18, 1.93) (Supplementary file 8; Table 4). Two studies reported data on the duration of hospital stay. Both were in favour of ACEIs/ARBs with Yang G. et al [25] reporting a significant reduction in the mean duration of hospital stay of 2.3 days (95%CI: -3.61, -0.99) with ACEIs/ARBs whilst Zeng et al [26] reporting a lower median duration of hospital stay of 21 days (IRQ: 15-25) with ACEIs/ARBs versus 22 days (IQR: 16-28) with non-ACEI/ARB use.

Use of a ventilator

Among pertinent studies, there was no significant association between these outcomes and the use of ACEIs/ARBs (OR:1.49; 95%CI: 0.80, 2.77; OR: 1.26; 95%CI: 0.84, 1.80), ACEIs (OR:1.01; 95%CI:0.03, 34.76; OR:1.15; 95%: 0.55, 2.38), or ARBs (OR:0.98; 95%CI: 0.08, 11.57; OR: 1.48; 95%CI: 0.91, 2.38) (Figure 9; Figure 10; Table 3). However, a significantly higher odds of ventilator use with ACEIs/ARBs among the European studies (OR: 3.34; 95%CI: 2.04, 5.48) and the USA (OR:1.52; 95%CI:1.17, 1.98) in contrast to significantly lower odds among those from Asia (OR:0.2; 95%CI: 0.04, 0.95) (Supplementary file 9, Table 4). Contrastingly, a significantly higher odds of ventilator use with ACEIs/ARBs was only observed among non-peer reviewed studies (OR:3.34; 95%CI: 2.04, 5.48) (Supplementary file 9, Table 1).

Other miscellaneous outcomes

Zhang et al [21] reported a significantly lower rate of septic shock (HR: 0.32; 95%CI: 0.13, 0.8) as well as non-significant lower rate of ARDS (HR: 0.65; 95%CI: 0.41, 1.04), acute kidney injury (HR:0.78; 95%CI: 0.37, 1.65), and cardiac injury (HR: 0.76; 95%CI: 0.44, 1.32) among ACEI/ARB users. Furthermore, Richardson S. et al [24], reported lower odds of hospital readmission with ACEIs/ARBs (OR: 0.77; 95%CI: 0.30, 1.94), albeit non-significant.

Publication bias

Results from the funnel plot (Supplementary file 10) and Egger's asymmetry test for the death outcome, which was the only outcome whereby >10 studies were included in the meta-analysis, indicated statistically insignificant evidence of publication bias (bias coefficient:0.85, 95%CI: -2.23, 3.93, p=0.445).

Discussion

The pooled analyses in this updated systematic review and meta-analysis indicated no evidence of any significant association between ACEIs/ARBs and any COVID-19 related clinical outcomes; however, the sub-group analyses revealed evidence of a negative impact of ACEIs/ARBs use and some COVID-19 related clinical outcomes such as higher odds of hospitalisation, ICU admission and ventilator use. Contrastingly, a positive impact in terms of lower odds of death/ICU admission, as a composite outcome, and a higher rate of hospital discharge. Furthermore, our study findings, for the first time, showed inter-class variations between ACEIs and ARBs effects on COVID-19 clinical outcomes with low quality evidence indicating lower risk of acquiring COVID-19, less severe COVID-19 infection, higher rate of ICU admission and ventilator use with ARBs but not ACEIs.

Our study findings also showed no significant association between ACEIs/ARBs and mortality, severe COVID-19 infection, or positive tests for COVID-19, in agreement with two previously published systematic reviews [29,30]. This was despite the inclusion of more recently published studies [18,27,40,41,49,50,53], which implies consistency of evidence. This is encouraging given the controversies surrounding hydroxychloroquine. Furthermore, these non-significant associations were also observed for additional COVID-19 related outcomes including ICU admission, hospitalisation, and hospital discharge. However, unlike the previous two systematic reviews [29,30], our study found evidence of associations between ACEI/ARB use and certain COVID-19 clinical outcomes. Whilst the pooled estimate of the sub-group analyses indicated a higher odds of ICU admission with ACEIs/ARBs among studies conducted in the USA [23,43,44] and peer-reviewed studies [23,25,44], all these studies were of poor quality and none performed adjusted analyses to account for potential confounders. Confounding by indication is of particular concern with comorbidities such as CVD and diabetes associated with more severe COVID-19 morbidity and mortality [4-6]. Similarly, the observed significant associations between ACEIs/ARBs use and high odds of ventilator use and hospital discharge rates were from Benelli *et al* [41] and Ip *et al* [27] and Zeng *et al* [26], respectively, all of which were non-peer reviewed, of poor quality and used crude analyses. Similarly, the studies in the pooled analyses that showed significant association of ARBs use and ICU admission [41,42], lower risk of acquiring COVID-19 infection [48], and severe infection [18,19] were of poor quality, used unadjusted/crude analyses, and/or non-peer reviewed. In terms of duration of hospital stay, Yang *et al* [25] and Zeng *et al* [26] both reported a reduction in hospital stay with ACEIs/ARBs; however, it was not possible to combine them in the meta-analysis as they used different measure of effects with the former reporting the outcome as a mean difference while the latter as a median.

On the other hand, our study findings showed some high-quality evidence on the association of ACEIs/ARBs and higher odds of hospitalisation but lower odds of death/ICU admission (as a composite endpoint). The higher odd of hospitalisation was observed in the sub-group analyses of studies conducted in the USA [43,44] although it should be noted that there was some heterogeneity (57.7%) between the

USA studies, used adjusted analyses [47], peer-reviewed [44] and of good quality [47]; whereas the studies for lower death/ICU admission were from Europe [40,45], used adjusted analyses and of good quality [40], although none of them were peer reviewed.

Several hypotheses have been suggested to explain the negative and positive effects of ACEIs/ARBs use on COVID-19 clinical outcomes. The former is thought to be related to ACEIs/ARBs potential ability to up-regulate ACE2, the cell entry point for COVID-19; hence facilitate COVID-19 cell entry and its subsequent infectivity/pathogenicity [55]; however, the evidence to date demonstrates ACE2's up-regulation consistently in cardiac and renal tissues in response to ARBs therapy but not ACEIs [4,56]; this observed difference between ARBs and ACEIs has been suggested to be due to the increased level of angiotensin-II, which occurs following ARBs treatment but not ACEIs, which in turn imposes an increased substrate load on ACE2 enzyme requiring its upregulation [57]. Importantly, it should be emphasised that evidence of ACEIs/ARBs induced ACE2 upregulation in the respiratory tracts, which is the key entry system for COVID-19, is lacking [56]. Furthermore, it should be noticed that alteration in angiotensin-II level, which is only one substrate of ACE2's multiple substrates, is unlikely to result in any meaningful differences in ACE2 substrate load, hence its upregulation [56]; additionally, the fact that people from various sexes, ages, and races are all susceptible to COVID-19 infection suggests that physiological expression of ACE2 might already be sufficient for COVID-19 infection; thus any further ACE2 upregulation might not have effects on the risk/severity of COVID-19 infection [25]. Together, these evidence indicate that the concerns around ACEIs/ARBs use in COVID-19 patients might be unjustifiable. On the other hand, the protective effect hypothesises on ACEIs/ARBs protecting against lung injury, through blockage of the harmful angiotensin II- AT_1R axis, which gets activated by impairment of ACE2 activity as a result of ACE2's downregulation results from ACE2's binding with COVID-19 virus; additionally, the corresponding increase in angiotensin II and angiotensin I, due to ACEIs/ARBs use, would activate the protective axis and hence reducing COVID-19 viral pathogenicity [4]. Genetic ACE2 polymorphism among some individuals has been also suggested as potential factor explaining, at least partially, the harmful effects on ACEIs/ARBs among COVId-19 patients [58]; but this needs further investigation.

Strengths and limitation

We believe this study is the first to provide a systematic, comprehensive and updated evaluation of the effects of ACEIs/ARBs on all the reported COVID-19 related clinical outcomes including exploration of inter-class differences between ACEIs and ARBs as well as multiple sub-group analyses, although we do acknowledge that some of the sub-group analyses only had 1-2 studies for some of the studied outcomes such as ICU admission and Death/ICU admission. However, our study has limitations. Since all included studies were observational studies, the effect of confounding including residual confounders cannot be ruled out. There is also the possibility that new studies have been published since our review. However, we included non-peer reviewed articles published in medRxiv to help address this.

Conclusion

There appears to be no evidence of association between ACEIs/ARBs use and a wide range of COVID-19 related clinical outcomes. However, good quality evidence exists for ACEIs/ARBs and higher odds of hospitalisation, lower odds of death/ICU admission (as composite endpoint); but low-quality evidence for higher ICU admission, ventilator use, hospital discharge and lower duration of hospital stay. Furthermore, there are evidence, albeit of poor quality, of differences between ACEIs and ARBs with the latter being associated with significantly higher ICU admission but lower COVID-19 infection risk and severity. Given the continuing controversial and paradoxical clinical studies' findings and hypotheses, we believe it is necessary to continue to evaluate the effects of ACEIs/ARBs on COVID-19 clinical outcomes especially as more randomised studies are reported.

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Conflict of interest

Nothing to declare

Author contributors

Study conception and design: all authors; data collection and management: NA, AL; data analysis and interpretation: AK, BG; manuscript writing and drafting: AK, NA; manuscript reviewing and revising as well as providing constrictive criticism and final approval: all authors

Ethical approval

Not required.

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Tables captions

Table 1. Study characteristics

	Population	Total *n*	Study Type	Exposure	*n* on RAAS inhibitors	Outcome(s)	Result (n or Odd Ratio + [95% confidence interval])
Bean D. et al (2020) [40]	All adult symptomatic inpatient testing positive for COVID-19.	1200	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	339	• Death • Critical care admission • Death or critical care admission	• n=106/399 vs. n=182/801 • n= 21/399 vs. n=106/801 • 0.63 (0.47-0.84)
Benelli G. et al (2020) [41]	Patients tested positive for COVID-19.	411	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	110	• Death • ICU admission • CPAP/NIV	• n= 25/110 vs 47/301 • n= 13/60 vs. 15/301 •n= 42/110 vs. 70/301
Bravi F. et al (2020) [45]	Patients diagnosis of COVID-19.	1603	Case-control	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	450	• Severe or very sever/lethal • Very severe lethal	• 0.58 (0.34-1.01) • 0.87 (0.50-1.49)
Chodick G. et al (2020) [49]	Patients with confirmed COVID-19.	1317	Cohort	ACEIs/ARBs users in patients with and without COVID-19	132	• Increased risk for COVID-19	• 1.19 (0.96-1.47)
Dauchet L. et al (2020) [42]*	Patients aged 35 years and over with suspected COVID-19.	288	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	109	• COVID-19+ • Hospitalisation • ICU admission	Data reported for ACE inhibitor and ARBs separately
DeSpiegeleer A. et al (2020) [50]	All residents at two elderly care homes with confirmed COVID-19.	154	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	30	• Serious COVID-19	• 0.48 (0.10-1.97)
Feng Y. et al (2020) [19]	Patients diagnosed with COVID-19.	467	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	33	Disease severity: • Moderate •Severe •Critical	• n= 29/33 **vs.**319/443 • n= 2/33 **vs.** 52/443 • n= 2/33 **vs.** 68/443
Feng Z. et al (2020) [51]	All adult patients with	564	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs	16	Disease severity	• 0.41 (0.05-3.19)

	confirmed COVID-19.			among COVID-19 patients			
Guo J. et al (2020) [28]	Patients with COVID-19	187	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	19	• Death	• n=7/ 19 vs. n=36/168
Ip Andrew et al (2020) [27]	Patients hospitalized with confirmed COVID-19	3017	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	NR	• Death (expired) • Discharged	• 1.6 [1.23-1.99] • n=323 vs. 407
Khawaja A. et al (2020) [52]	Patients hospitalized with COVID -19	605	Cohort	ACEIs/ARBs users in patients with and without COVID-19	125	• Hospitalisation with COVID-19	Data reported for ACE inhibitor and ARBs separately
Khera R. et al (2020) [46]	Patients receiving anti-hypertensive agents and tested positive for COVID-19.	2263	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	852	• Hospitalization • Mortality	Data reported for ACE inhibitor and ARBs separately
Li J. et al (2020) [24]	Patients with COVID-19 and hypertension	1178	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	115	• Severity • Death	• n=57/115 vs. 116/247 • n=21/115 vs. 56/247
Liu Y. et al (2020) [18]	All patients were diagnosed with COVID-19 and hypertension	78	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	12	• Disease severity	Data reported for ACE inhibitor and ARBs separately
Mancia G. et al (2020) [21]	Patients 40 years of age or older with a Positive test of COVID -19	6272	Case-control	ACEIs/ARBs users in patients with and without COVID-19	2896	• Critical or fatal of clinical manifestations	Data reported for ACE inhibitor and ARBs separately
Mehta N. et al (2020) [44]	Patients tested for COVID-19 and had ACEI	18472	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs	212	• COVID-19+ • Hospital admission	• 0.97[0.81-1.15] • 1.93 (1.38-2.71)

	or ARB prescribed.			among COVID-19 patients		• ICU-admission • Use of ventilator • Hospitalisation • Hospital discharge • Severity of disease • Death	• 1.64 (1.07-2.51) • 1.32 (0.80-2.18) • 4 days vs. 2 days • 20 days vs. 16.5 days • OR:0.33[0.09-1.31] • n=0/17 vs. n=1/25
Meng J. el al (2020) [17]	Patients with positive COVID-19.	42	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	17		
Raisi-Estabragh Z. et al (2020) [53]	Individuals tested for COVID-19 aged 40-69 years old.	1474	Cohort	ACEIs/ARBs users in patients with and without COVID-19	312	COVID+	• 0.956[0.695-1.316]
Rentsch Ch. et al (2020) [43]	Veterans aged 54-75 years with positive COVID-19 test	585	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	255	• COVID-19+ • Hospitalisation • ICU admission	• 0.93[0.78-1.23] • 1.24[0.79-1.95] • 1.69[1.01-2.84]
Reynolds H. et al (2020) [22]	Patients who were tested for COVID-19.	12594	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	2319	• COVID-19+ • Severity of COVID-19	• 1110/1909 vs. 1101/1909 • 275/1110 vs. 274/1101
Rhee S. et al (2020) [54]	Patients with confirmed COVID-19	832	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	327	•ICU admission or death	• 0.599[0.251-1.431].
Richardson S. et al (2020) [23]	All patients who hospitalized with COVID-19 infection.	5700	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	413	• Invasive mechanical ventilation • ICU care • Readmission • Discharged home • Death	• n= 79/413 vs. n=122/953 • n= 87/413 vs. 141/953 • n=6/413 vs. n=18/953 • n=261/413 vs. 639/953 • n=130/413 vs. 254/953
Rossi P. et al (2020) [47]	All symptomatic patients who tested positive for COVID-19.	2653	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	450	• Death • Hospitalisation	• 0.8[0.50-1.3] • 1.12 [0.82-1.54]
Yan H. et al (2020) [48]	Patients with confirmed diagnosis of COVID -19 infection.	610	Case-control	ACEIs/ARBs users in patients with and without COVID-19	NR	• COVID-19+ • Disease severity of COVID-19 severe + critical vs. mild + common	Data reported for ACE inhibitor and ARBs separately

Yang G. et al (2020) [25]	Patients with confirmed COVID-19.	462	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	43	•Tested positive for COVID-19 • Days patient remained in hospital (mean ±SD) • Critical severity • Death	• n=43 vs. n=83 • 35.2±12.8 vs. 37.5±12.3. • n=4 vs. n=19 • n=2 vs. n=11
Zeng Zh. et al (2020) [26]	Adult patients with suspected and confirmed cases of COVID-19.	274	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	28	• Mortality • length of hospital stays (days) • discharge rate • hospitalization rate. • Tested positive for COVID • Severe pneumonia	• n=2/28 vs. n=5/47 • n=21(15.25) vs. n=22 (16-28) • n=21/28 vs, n=29/47 • n=5/28 vs. n=13/47 • n=20/28 vs. n=31/47 • n=15/28 vs. n=15/47
Zhang P.et al (2020) [20]	Patients diagnosed with COVID-19,	1128	Cohort	ACEIs/ARBs vs. non-ACEIs/ARBs among COVID-19 patients	188	• Mortality • Acute respiratory distress syndrome • Septic shock • Acute kidney injury • Cardiac injury	• 0.37 [0.15-0.89] • 0.65 [0.41-1.04] • 0.32 [0.13-0.80] • 0.78 [0.37-1.65] • 0.78 [0.44-1.32]

(Note) *: this study reported data from two cohorts; hence it is included twice in the analyses; ACEIs: Angiotensin-converting-enzyme inhibitors; ARBs: Angiotensin II receptor blockers; COVID: coronavirus disease; CPAP: continuous positive airway pressure; ICU: intensive care unit; n: number of patients; NIV: non-invasive ventilation; NR: not reported; OR: odds ratio; RAAS: Renin-Angiotensin-Aldosterone System; SD: standard deviation

Table 2 Quality assessment score of the studies included into the systematic review and meta-analysis based on the using the Newcastle-Ottawa Scale

Cohort studies													
N	**Author (Month, year)**	**Selection**				**Comparability**		**Outcome**			**Final score**	**Score Quality****
1	Bean D. et al., (May 2020) [40]	B*	C	A*	A*	Demographic*	Comorbidities*	B*	A*	C	7	Good
2	Benelli G. et al., (April 2020) [41]	B*	C	A*	A*	-	-	B*	No	C	4	Poor
3	Chodick G. et al., (May 2020) [49]	B*	C	A*	A*	Demographic*	Comorbidities*	B*	NA	D	6	Poor
4	DeSpiegeleer A. et al., (May 2020) [50]	B*	C	A*	A*	Demographic*	Comorbidities*	B*	NA	D	6	Poor
5	Feng Y. et al., (April 2020) [19]	B*	C	A*	A*	-	-	B*	NA	D	4	Poor
6	Feng Z. et al., (April 2020) [51]	B*	C	A*	A*	-	-	B*	NA	D	4	Poor
7	Khawaja A. et al., (May 2020) [52]	A*	A*	A*	A*	Demographic*	Comorbidities*	B*	NA	D	7	Poor
8	Khera R. et al., (2020) [46]	B*	A*	A*	A*	-	-	B*	NA	D	5	Poor
9	Li J. et al., (April 2020) [24]	B*	C	A*	A*	-	-	B*	NA	D	4	Poor
10	Dauchet L. et al., (May 2020) [42]	B*	A*	A*	A*	-	-	B*	NA	D	5	Poor
11	Ip Andrew et al., (April 2020) [27]	B*	C	A*	A*	-	-	B*	NA	D	4	Poor
12	Liu Y. et al., (March 2020) [18]	A*	C	A*	A*	-	-	B*	NA	D	4	Poor
13	Mehta N. et al., (May 2020) [44]	A*	A*	A*	A*	-	-	B*	NA	D	5	Poor
14	Raisi-Estabragh Z. et al., May 2020) [53]	B*	A*	A*	A*	-	-	B*			5	Poor
15	Rhee S. et al., (May 2020) [54]	A*	A*	A*	A*	Demographic*	Comorbidities*	B*	NA	D	7	Poor
16	Yang G. et al., (May 2020) [25]	B*	A*	A*	A*	-	-	B*	B	D	5	Poor
17	Zeng Zh.et al., (April 2020) [26]	B*	A*	A*	A*	-	-	B*	A*	A*	7	Poor
18	Zhang P. et al., (April 2020) [20]	A*	A*	A*	A*	Demographic*	Comorbidities*	B*	NA	D	7	Poor
19	Rossi P. et al., (April 2020) [47]	A*	C	A*	A*	Demographic*	Comorbidities*	B*	A*	A*	8	Good

20	Reynolds H. et al., (May 2020) [22]	B*	A*	A*	A*	Demographic*	Comorbidities*	B*	NA	D	7	Poor
21	Rentsch Ch. et al., (April 2020) [43]	B*	C	A*	A*	-	-	B*	NA	D	4	Poor
22	Meng J. el al., (March 2020) [17]	B*	C	A*	A*	-	-	B*	NA	D	4	Poor
23	Guo J. et al., (May 2020) [28]	A*	C	A*	A*	-	-	B*	NA	D	4	Poor
24	Richardson S. et al., (April 2020) [23]	A*	C	A*	A*	-	-	B*	B	D	4	Poor
Case-control studies												
25	Bravi F. et al., (May 2020) [45]	A*	A*	A*	A*	-	-	A*	A*	C	6	Poor
26	Mancia G. et al., (May 2020) [21]	A*	A*	A*	A*	-	Comorbidities *	A*	A*	C	7	Good
27	Yan H. et al., (April 2020) [48]	A*	A*	A*	A*	Demographic*	-	B*	A*	D	6	Good

(Note) **Studies were classified into good quality (3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain), fair quality (2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain) and poor quality (0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain) (33)

Table 3. Meta-analyses pooled estimates with 95%CI of the effects of ACEIs/ARBs on COVID-19 related clinical outcomes

Outcomes	ACEIs/ARBs	p-value	ACEIs	p-value	ARBs	P-value
Death	0.973 (0.746, 1.269)	0.84	1.049 (0.751, 1.464)	0.781	1.181 (0.983, 1.418)	0.076
Number of studies	11		2		2	
I-squared	65.5%	0.001	26.3%	0.244	0.6%	0.316
ICU	1.086 (0.652, 1.809)	0.75	0.945 (0.65, 1.376)	0.769	1.49 (1.126, 1.973)	0.005
Number of studies	6		3		3	
I-squared (p-value)	84.4%	<0.001	4.9%	0.349	0%	0.475
Death/ICU	0.67 (0.524, 0.857)	0.001	0.888 (0.694, 1.136)	0.345	0.83 (0.65, 1.061)	0.136
Number of studies	3		2		2	
I-squared (p-value)	0%	0.572	0%	0.726	0%	1.000
Risk of COVID-19	1.014 (0.935, 1.099)	0.745	1.133 (1.417, 21.27)	0.273	0.557 (0.107, 2.895)	0.46
Number of studies	7		3		2	
I-squared (p-value)	0%	0.75	0%	0.457	97.9%	<0.001
Severe COVID-19	0.782 (0.529, 1.154)	0.215	0.718 (0.264, 1.955)	0.517	0.506 (0.247, 1.036)	0.062
Number of studies	6		3		3	
I-squared (p-value)	43.3%	0.117	0%	0.799	18%	0.296
Severe pneumonia	1.285 (0.237, 6.958)	0.771	NA		NA	
Number of studies	2					
I-squared (p-value)	57.5%	0.125				
Hospitalisation	1.153 (0.806, 1.65)	0.436	1.077 (0.791, 1.465)	0.638	0.907 (0.74, 1.112)	0.349
Number of studies	5		5		5	
I-squared (p-value)	74.5%	0.003	63.7%	0.026	0%	0.965
Hospital discharge	1.213 (0.739, 1.991)	0.446	NA		NA	
Number of studies	3					
I-squared (p-value)	82.2%	0.004				
Ventilator use	1.492 (0.804, 2.77)	0.205	1.014 (0.03, 34.758)	0.994	0.985 (0.084, 11.57)	0.990
Number of studies	4		2		2	
I-squared (p-value)	80.7%	0.001	64.7%	0.092	88.6%	0.003
ICU/ventilator use	1.225 (0.836, 1.795)	0.298	1.149 (0.554, 2.382)	0.709	1.467 (0.907, 2.373)	0.118
Number of studies	10		5		5	
I-squared (p-value)	83.2%	<0.001	75.2%	0.003	66.2%	<0.001
(Note) NA: not applicable indicating no enough studies to perform meta-analyses						

Table 4. Sub-group meta-analyses pooled estimates with 95%CI of the effects of ACEIs/ARBs on COVID-19 related clinical outcomes

	Death (n=15)		
	ACEIs/ARBs	**ACEIs**	**ARBs**
Adjusted outcome measure			
Adjusted OR	0.973 (0.260, 1.660)	NA	NA
Crude OR	1.048 (0.772, 1.424)	1.049 (0.751, 1.464)*	1.181 (0.983, 1.418)*
Number of studies	2 vs 9	0 vs. 2	0 vs. 2
Peer reviewed article?			
Yes	0.894 (0.522, 1.533)	NA	NA
No	1.004 (0.716, 1.408)	1.049 (0.751, 1.464)*	1.181 (0.983, 1.418)*
Number of studies	6 vs. 5	0 vs. 2	0 vs. 2
Study's quality			
Good quality	1.113 (0.884, 1.400)	NA	NA
Poor quality	0.915 (0.627, 1.336)	1.049 (0.751,1.464)*	1.181 (0.983,1.418)*
Number of studies	2 vs. 9	0 vs. 2	0 vs. 2
Study's country			
Europe	1.176 (0.932, 1.483)	1.523 (0.728, 3.185)	1.645 (0.838, 3.229)
USA	0.92 (0.494, 1.714)	0.97 (0.811, 1.161)	1.15 (0.954, 1.386)
Asia	0.753 (0.401, 1.413)	NA	NA
Number of studies	3 vs. 2 vs. 6	1 vs. 1 vs. 0	1 vs. 1 vs. 0
		ICU admission (n=12)	
Adjusted outcome measure			
Adjusted OR	NA	NA	NA
Crude OR	1.086 (0.652, 1.809)*	0.945 (0.650, 1.376)*	1.490 (1.126, 1.973)*
Number of studies	0 vs. 6	0 vs. 3	0 vs. 3
Peer reviewed article?			
Yes	1.560 (1.234, 1.972)	NA	NA
No	0.762 (0.295, 1.972)	0.945 (0.650, 1.376)*	1.490 (1.126, 1.973)*
Number of studies	3 vs. 3	0 vs. 3	0 vs. 3
Study's quality			
Good quality	0.364 (0.224, 0.591)	NA	NA
Poor quality	1.445 (0.133, 1.843)	0.945 (0.650, 1.376)*	1.490 (1.126, 1.973)*
Number of studies	1 vs. 5	0 vs. 3	0 vs. 3
Study's country			
Europe	0.495 (0.253, 0.966)	0.945 (0.650, 1.376)*	1.490 (1.126, 1.973)*
USA	1.591 (1.277, 1.983)	NA	NA
Asia	1.439 (0.600, 3.453)	NA	NA
Number of studies	2 vs. 3. vs. 1	3 vs. 0. vs. 0	3 vs. 0. vs. 0
		Death/ICU admission (n=7)	
Adjusted outcome measure			

Adjusted OR	0.630 (0.471, 0.842)	NA	NA
Crude OR	0.783 (0.493, 1.243)	0.888 (0.694, 1.136)*	0.830 (0.650, 1.061)*
Number of studies	1 vs. 2	0 vs. 2	0 vs. 2
Peer reviewed article?			
Yes	NA	0.910 (0.690, 1.210)	0.830 (0.630, 1.100)
No	0.670 (0.524, 0.857)*	0.820 (0.490, 1.360)	0.830 (0.500, 1.400)
Number of studies	0 vs. 3	1 vs. 1	1 vs. 1
Study's quality			
Good quality	0.630 (0.471, 0.842)	0.910 (0.687, 1.205)	0.830 (0.628, 1.097)
Poor quality	0.783 (0.493, 1.243)	0.820 (0.492, 1.366)	0.830 (0.496, 1.389)
Number of studies	1 vs. 2	1 vs. 1	1 vs. 1
Study's country			
Europe	0.679 (0.520, 0.887)	0.888 (0.694, 1.136)	0.830 (0.650, 1.061)
USA	NA	NA	NA
Asia	0.599 (0.251, 1.430)	NA	NA
Number of studies	2 vs. 0 vs. 1	2 vs. 0 vs. 0	2 vs. 0 vs. 0
		Risk of COVID-19 infection (n=12)	
Adjusted outcome measure			
Adjusted OR	1.190 (0.962, 1.473)	1.180 (0.867, 1.605)	1.290 (0.930, 1.790)
Crude OR	0.986 (0.904, 1.077)	1.015 (0.620, 1.662)	0.240 (0.170, 0.340)
Number of studies	1 vs. 6	1 vs. 2	1 vs. 1
Peer reviewed article?			
Yes	1.030 (0.941, 1.128)	1.180 (0.867, 1.605)	1.290 (0.930, 1.790)
No	0.948 (0.790, 1.138)	1.015 (0.620, 1.662)	0.240 (0.170, 0.340)
Number of studies	4 vs. 3	1 vs. 2	1 vs. 1
Study's quality			
Good quality	NA	0.650 (0.265, 1.597)	0.240 (0.170, 0.339)
Poor quality	1.014 (0.935, 1.099)*	1.176 (0.933, 1.481)	1.290 (0.930, 1.790)
Number of studies	0 vs. 7	1 vs. 2	1 vs. 1
Study's country			
Europe	0.956 (0.695, 1.316)	1.170 (0.825, 1.660)	NA
USA	0.99 (0.901, 1.087)	NA	NA
Asia	1.131 (0.942, 1.358)	1.023 (0.622, 1.684)	0.557 (0.107, 2.895)*
Number of studies	1 vs. 3 vs. 3	1 vs. 0 vs. 2	0 vs. 0 vs. 2
		Severe COVID-19 (n=12)	
Adjusted outcome measure			
Adjusted OR	0.480 (0.108, 2.130)	NA	NA
Crude OR	0.795 (0.525, 1.206)	0.718 (0.264, 1.955)*	0.506 (0.247, 1.036)*
Number of studies	1 vs. 5	0 vs. 3	0 vs. 3
Peer reviewed article?			
Yes	0.895 (0.614, 1.303)	0.595 (0.067, 5.296)	0.333 (0.069, 1.607)

No	0.387 (0.144, 1.040)	0.755 (0.245, 2.328)	0.509 (0.176, 1.474)
Number of studies	4 vs. 2	1 vs, 2	1 vs. 2
Study's quality			
Good quality	NA	1.230 (0.190, 7.946)	0.770 (0.362, 1.638)
Poor quality	0.782 (0.529, 1.154)*	0.578 (0.176, 1.893)	0.283 (0.101, 0.792)
Number of studies	0 vs. 6	1 vs. 2	1 vs. 2
Study's country			
Europe	0.480 (0.108, 1.130)	NA	NA
USA	0.994 (0.820, 1.205)	NA	NA
Asia	0.513 (0.216, 1.216)	0.718 (0.264, 1.955)*	0.506 (0.247, 1.036)*
Number of studies	1 vs. 1 vs. 4	0 vs. 0 vs. 3	0 vs. 0 vs. 3
		Severe pneumonia (n=2)	
Adjusted outcome measure			
Adjusted OR	0.410 (0.050, 3.275)	NA	NA
Crude OR	2.462 (0.939, 6.452)	NA	NA
Number of studies	1 vs. 1		
Peer reviewed article?			
Yes	NA	NA	NA
No	1.285 (0.237, 6.958)	NA	NA
Number of studies	0 vs. 2		
Study's quality			
Good quality	NA	NA	NA
Poor quality	1.285 (0.237, 6.958)	NA	NA
Number of studies	0 vs. 2		
Study's country			
Europe	NA	NA	NA
USA	NA	NA	NA
Asia	1.285 (0.237, 6.958)		
Number of studies	0 vs. 0 vs. 2		
		Hospitalisation (n=15)	
Adjusted outcome measure			
Adjusted OR	1.300 (1.113, 1.518)	1.170 (0.900, 1.520)	1.0 (0.702, 1.424)
Crude OR	1.032 (0.561, 1.897)	1.056 (0.684, 1.631)	0.865 (0.674, 1.109)
Number of studies	1 vs. 4	1 vs. 4	1 vs. 4
Peer reviewed article?			
Yes	1.930 (1.377, 2.705)	NA	NA
No	0.977 (0.647, 1.474)	1.077 (0.791, 1.465)*	0.907 (0.740, 1.112)*
Number of studies	1 vs. 4	0 vs. 5	0 vs. 5
Study's quality			
Good quality	1.300 (1.113, 1.518)	NA	NA
Poor quality	1.032 (0.561, 1.897)	1.077 (0.791, 1.465)*	0.907 (0.740, 1.112)*

Number of studies	1 vs. 4	0 vs. 5	0 vs. 5
Study's country			
Europe	0.907 (0.413, 1.992)	1.181 (0.843, 1.656)	0.922 (0.721, 1.179)
USA	1.589 (1.033, 2.443)	0.77 (0.527, 1.124)	0.877 (0.611, 1.258)
Asia	0.569 (0.178, 1.815)	NA	NA
Number of studies	2 vs. 2 vs. 1	4 vs. 1 vs. 0	4 vs. 1 vs. 0
		Hospital discharge (n=3)	
Adjusted outcome measure			
Adjusted OR	NA	NA	NA
Crude OR	1.213 (0.739, 1.991)	NA	NA
Number of studies	0 vs. 3		
Peer reviewed article?			
Yes	0.844 (0.663, 1.074)	NA	NA
No	1.513 (1.184, 1.935)	NA	NA
Number of studies	1 vs. 2		
Study's quality			
Good quality	NA	NA	NA
Poor quality	1.213 (0.739, 1.991)	NA	NA
Number of studies	0 vs. 3		
Study's country			
Europe	NA	NA	NA
USA	1.122 (0.641, 1.964)	NA	NA
Asia	1.862 (0.659, 5.26)	NA	NA
Number of studies	0 vs. 2 vs. 1		
		Ventilator use (n=8)	
Adjusted outcome measure			
Adjusted OR	NA	NA	NA
Crude OR	1.492 (0.804, 2.770)	1.014 (0.03, 34.758)	0.985 (0.084, 11.57)
Number of studies	0 vs. 4	0 vs. 2	0 vs. 2
Peer reviewed article?			
Yes	1.141 (0.606, 2.150)	0.078 (0.001, 6.878)	0.251 (0.053, 1.185)
No	3.338 (2.035, 5.475)	3.603 (1.889, 6.872)	3.129 (1.699, 5.761)
Number of studies	1 vs. 3	1 vs. 1	1 vs. 1
Study's quality			
Good quality	NA	NA	NA
Poor quality	1.492 (0.804, 2.770)	1.014 (0.030, 34.758)	0.985 (0.084, 11.570)
Number of studies	0 vs. 4	0 vs. 2	0 vs. 2
Study's country			
Europe	3.338 (2.035, 5.475)	3.603 (1.889, 6.872)	3.129 (1.699, 5.762)
USA	1.524 (1.171, 1.985)	NA	NA
Asia	0.202 (0.043, 0.947)	0.078 (0.001, 6.469)	0.251 (0.053, 1.187)

Number of studies	1 vs. 2 vs. 1	1 vs. 0 vs. 1	1 vs. 0 vs. 1

(Note) *Indicates that the pooled estimate is the same as the overall analyses because all the studies were in one group; NA: not applicable indicating that no studies were available to perform meta-analyses for these outcomes;

Figures captions

Figure 1 Study selection

Figure 2 Forest plot depicting pooled estimates for the association between mortality and the three level of renin-angiotensin system drug exposure (ACEIs/ARBs, ACEIs, ARBs)

Figure 3 Forest plot depicting pooled estimates for the association between Intensive Care Unit admission and the three level of renin-angiotensin system drug exposure (ACEIs/ARBs, ACEIs, ARBs)

Figure 4 Forest plot depicting pooled estimates for the association between the composite outcome of mortality/ Intensive Care admission and the three level of renin-angiotensin system drug exposure (ACEIs/ARBs, ACEIs, ARBs)

Figure 5 Forest plot depicting pooled estimates for the association between risk of acquiring COVID-19 infection and the three level of renin-angiotensin system drug exposure (ACEIs/ARBs, ACEIs, ARBs)

Figure 6 Forest plot depicting pooled estimates for the association between developing severe COVID-19 infection and the three level of renin-angiotensin system drug exposure (ACEIs/ARBs, ACEIs, ARBs)

Figure 7 Forest plot depicting pooled estimates for the association between hospitalisation and the three level of renin-angiotensin system drug exposure (ACEIs/ARBs, ACEIs, ARBs)

Figure 8 Forest plot depicting pooled estimate for the association between hospital discharge and ACEIs/ARBs use

Figure 9 Forest plot depicting pooled estimates for the association between use of ventilator and the three level of renin-angiotensin system drug exposure (ACEIs/ARBs, ACEIs, ARBs)

Figure 10 Forest plot depicting pooled estimates for the association between use of ventilator/Intensive Care Unit admission and the three level of renin-angiotensin system drug exposure (ACEIs/ARBs, ACEIs, ARBs)

Supplementary files' captions and legends

Supplementary file 1. Search strategy used in the database searches

Supplementary file 2. Forest plot depicting sub-group analyses pooled estimates for the association between mortality and ACEIs/ARBs use sub-grouped by A) country; B) methodological quality; C) peer-review status; and D) type of analyses (crude vs. adjusted)

Supplementary file 3. Forest plot depicting sub-group analyses pooled estimates for the association between Intensive Care Unit admission and ACEIs/ARBs use sub-grouped by A) country; B) methodological quality; C) peer-review status

Supplementary file 4. Forest plot depicting sub-group analyses pooled estimates for the association between the composite outcome of mortality/ Intensive Care admission and ACEIs/ARBs use sub-grouped by A) country; B) methodological quality; C) type of analyses (crude vs. adjusted)

Supplementary file 5A. Forest plot depicting sub-group analyses pooled estimates for the association between risk of acquiring COVID-19 infection and ACEIs/ARBs use sub-grouped by A) country; B) peer-review status; and C) type of analyses (crude vs. adjusted)

Supplementary 5B. Forest plot depicting sub-group analyses pooled estimates for the association between risk of acquiring COVID-19 infection and ACEIs use sub-grouped by A) country; B) methodological quality; C) peer-review status; and D) type of analyses (crude vs. adjusted)

Supplementary 5C. Forest plot depicting sub-group analyses pooled estimates for the association between risk of acquiring COVID-19 infection and ARBs use sub-grouped by A) methodological quality; B) peer-review status; and C) type of analyses (crude vs. adjusted)

Supplementary file 6. Forest plot depicting sub-group analyses pooled estimates for the association between developing severe COVID-19 infection and ACEIs/ARBs use sub-grouped by A) country; B) peer-review status; and C) type of analyses (crude vs. adjusted)

Supplementary file 7. Forest plot depicting sub-group analyses pooled estimates for the association between hospitalisation and ACEIs/ARBs use sub-grouped by A) country; B) methodological quality; C) peer-review status; and D) type of analyses (crude vs. adjusted)

Supplementary file 8. Forest plot depicting sub-group analyses pooled estimates for the association between hospital discharge and ACEIs/ARBs use sub-grouped by A) country; B) peer-review status

Supplementary file 9. Forest plot depicting sub-group analyses pooled estimates for the association between ventilator use and ACEIs/ARBs use sub-grouped by A) country; B) peer-review status

Supplementary file 10. Publication bias funnel plot for studies evaluated death outcome